| Examiner-Initiated Interview Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/724,000 | POLVERINO ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1643 | |

**All Participants:** **Status of Application:** _____

(1) *Stephen L. Rawlings, Ph.D.*. (3) *Kevin Noonan, Ph.D.*

(2) *Jason Derry, Ph.D.*. (4) _____.

**Date of Interview:** *10 March 2006* **Time:** _____

**Type of Interview:**
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☐ No
If Yes, provide a brief description: .

**Part I.**

Rejection(s) discussed:
*written description; prior art*

Claims discussed:
*9, 13, 14, 16, 46, 47, 57, and 59-61*

Prior art documents discussed:
*US 2002/0068319 A1*

**Part II.**

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
*See Continuation Sheet*

**Part III.**

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

(Examiner/SPE Signature) (Applicant/Applicant's Representative Signature – if appropriate)

Continuation of Substance of Interview including description of the general nature of what was discussed: The Examiner telephoned to explain reasons that the allowability of claims 9, 13, 16, 57, 59, and 60 will be withdrawn and to suggest amending the claims to obviate the grounds of rejection set forth under 35 U.S.C. 112, first paragraph, as failing to meet the written description requirement. The Examiner also discussed newly discovered prior art, which teaches the polypeptide of SEQ ID NO: 5. It was agreed that the Examiner would prepare an Office action to provide Applicant with the opportunity to more carefully consider those gronds of rejection and determine how best to respond..

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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January 14, 2003

TO: Principal Investigators for Human Gene Transfer Trials Employing Retroviral Vectors

FROM: Amy P. Patterson, M.D.
Director
NIH Office of Biotechnology Activities

SUBJECT: Notification of a Serious Adverse Event

You are undoubtedly aware of a widely reported serious adverse event -- a T cell leukemia (TLL) -- that occurred last summer in a French trial studying human gene transfer as a possible treatment for X-linked Severe Combined Immunodeficiency (X-SCID). The purpose of this memorandum is to notify you that a second subject in that trial has developed a TLL. As was true of the first event, this second event is directly related to the retroviral-mediated insertion of the gene product, according to preliminary data described by the investigators. The NIH is notifying investigators employing retroviral vectors of the facts currently known about this event, since this information is vital to promoting the safe conduct of trials and to ensuring fully informed consent to potential research participants. **Moreover, the NIH is urging investigators conducting retroviral-mediated gene transfer in hematopoietic cells to discontinue enrollment and administration of the experimental agent** until new data are available, the possible etiology and risks of these adverse events are considered by the appropriate federal advisory committees (including the NIH Recombinant DNA Advisory Committee), and recommendations emerge. Investigators should also know that the FDA has issued a clinical hold for a subset of these trials – those using retrovirally transduced hematopoietic stem cells.

**Description of the Trial**

The trial involved transducing the subjects' $CD34^+$ cells *ex vivo* with a defective Moloney murine leukemia retroviral vector (MFG) containing the common gamma chain ($\gamma c$) gene for the cytokine receptors IL-2R, IL-4R, IL-7R, IL-9R and IL-15R. These cytokines are responsible for delivery of growth, survival and differentiation signals to the early lymphoid progenitors. The strategy of this experimental approach was to correct the early block in T-cell and natural killer (NK) lymphocyte differentiation ($\gamma c$ maps at Xq13).

A total of eleven subjects were enrolled in this trial. Nine subjects experienced significant restoration of their immune systems. Two of the nine have experienced serious adverse events that appear directly related to the gene transfer intervention.

**First Serious Adverse Event**

The first serious adverse event in this trial was examined by the NIH Recombinant DNA Advisory Committee (RAC) at its December 2002 meeting and safety symposium. The child experiencing this event developed a gamma-delta T-cell receptor (TCR) positive monoclonal TLL. The TLL was shown to be a direct result of the insertion of the gene transfer product into LMO-2, an oncogene responsible for childhood leukemia. The development of cancer due to insertional mutagenesis was known to be theoretically possible, but presumed to be unlikely based on previous experience with trials using retroviral vectors.

Of note, there were several factors pertinent to this subject's case that were considered as possibly contributing to the event, including an intercurrent varicella infection, a 6:13 chromosomal translocation, and a family history of childhood cancer. Investigators are continuing to explore the significance of these factors, if any.

At its December meeting, the RAC concluded that the gene transfer intervention was a cause of the leukemia, but that it was too early to draw any conclusions about the broader relevance of this event to other retroviral studies. Nonetheless, the RAC stated that appropriate informed consent and long-term monitoring of participants would be key to ensuring that all potential participants were fully aware of this event and necessary for scrutinizing the safety of trials studying gene transfer approaches to SCID. More information about the RAC's discussions and conclusions concerning this event can be found at: http://www.webconferences.com/nihoba/4-6_december_02.html

**Second Serious Adverse Event**

In late December 2002, the NIH received a report that a second child in the trial developed a TLL. This event bears certain similarities to, as well as differences from, the first case. Unlike the first serious adverse event, this subject has developed an alpha-beta (not gamma-delta) TCR positive TLL that is comprised of three T cell clones (not just one). Also, unlike the first child, this subject did not exhibit any intercurrent infections and is not presently known to have a family medical history that would be predisposing to cancer.

Similar to the situation of the first child, this second child was treated at a very early age (three months vs. one month for the first child) with a high dose of $CD34^+$ gamma-c+ cells. The two children who have developed the TLL received the highest doses of gene transfer product in this trial. The second child developed TLL at about the same time post treatment as the first child (approximately 3 years post-infusion). The retroviral-gamma-c gene transfer product has integrated into the same site in all three clones, which in this case is near (not in) LMO-2. Both children have responded to chemotherapy and now have T cell counts that are significantly reduced.

The investigators are conducting further analyses to obtain more data and facilitate a better understanding of this event.

**Enrollment in Retroviral Studies Using Hematopoietic Cells**

These two instances of insertional mutagenesis directly related to retroviral-mediated gene transfer are significant and warrant immediate notification of the scientific community working in this field as well as the institutional committees responsible for oversight of such trials. The evidence to date suggests that, due to higher transduction rates, hematopoietic cells may be particularly vulnerable to this type of event. Therefore, NIH is urging investigators conducting retroviral-mediated gene transfer into hematopoietic cells to discontinue enrollment and administration of the experimental agent until new data are available, the possible etiology and risks of these adverse events are considered by the appropriate federal advisory committees (including the RAC), and recommendations emerge.

The NIH believes that this development warrants an abundance of caution while further examination of the scientific, safety, and ethical issues associated with trials using retroviral-mediated gene transfer into hematopoietic cells proceeds.

**Next Steps**

NIH, through OBA, is working closely with the investigators in this trial, as well as other scientists in this field, to gather and analyze all available data. An expedited meeting of the RAC will be convened on January 17, 2002 to allow for an immediate and public scientific exploration of all known facts. The details of this meeting will be announced shortly on the OBA Web site at http://www4.od.nih.gov/oba/RAC/meeting.html, over the OBA listserv, and in the *Federal Register*. Findings by the RAC with respect to this event will be disseminated to the scientific community and broader public and also will be available on the OBA Web site.

The NIH will be organizing a safety symposium on retroviral-mediated gene transfer as part of the March 5-7, 2003 RAC meeting. This meeting will be open to the public and publicized as above. Broad participation is encouraged.

In taking all these steps, the NIH is coordinating with the Food and Drug Administration (FDA) and working through major scientific associations, such as the American Society for Gene Therapy, to keep the investigator community informed.

cc: NIH Recombinant DNA Advisory Committee
Institutional Biosafety Committees at relevant institutions (please forward a copy of this correspondence to your Institutional Review Board)
Food and Drug Administration Center for Biologics Evaluation and Research
HHS Office for Human Research Protections